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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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MINTZ, LEVIN, COHN, FERRIS, GLOVSKY
AND POPEO, P.C.
ONE FINANCIAL CENTER
BOSTON, MA 02111

EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 07/12/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/826,077	STANTON ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *3,5 and 7-9* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6 and 10-18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *15 April 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *see box 6*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: IDS of 8/04,12/04,3/06,4/06 & 5/06.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of Group I, claims 1-18, the further election of PSMA as the target and the species elections of aptamers as targeting moieties, small molecule therapeutic agents, vinca alkaloid and desacetyl vinblastine 3-carboxhydrazide in the reply filed on April 24, 2006 is acknowledged.

Claims 3, 5 and 7-9 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 24, 2006.

Claims 1, 2, 4, 6 and 10-18 are examined on the merits.

Priority

The specification of the prior filed application, 10/600,007, does not provide support for aptamer-drug conjugates having the formula shown in claim 10, nor does it provide support for aptamer-drug conjugates comprising DAVCH, Boc-protected amines, dendrimers or comb polymers. Therefore, the filing date according the subject matter of claims 10-18 is April 15, 2004, the filing date of the instant application. If applicant believes the disclosure of the prior filed application provides support for this subject matter, it should be pointed out with particularity in any response to this action.

Specification

The use of the trademark SELEX has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

It is noted that some occurrences of this term are noted as being a trademark, but other instances, for example on pages 10 and 12, do not properly indicate the trademarked status of this term.

Claim Objections

Claims 4, 12, 14 and 15 are objected to because of the following informalities: each of these claims contains non-elected subject matter. Claim 12 is additionally objected to for the use of an abbreviation without identification of the meaning of the abbreviation. For the sake of clarity it is recommended that the target described as PSMA be defined.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to

identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claims 1, 2, 4 and 6 of this application conflict with claims 1, 2, 4 and 6 of Application No. 10/600,007. 37 CFR 1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP § 822.

Claims 1, 2, 4 and 6 are provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claims 1, 2, 4 and 6 of copending Application No. 10/600,007. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented.

Claims 1, 2, 4 and 6 are directed to the same invention as that of claims 1, 2, 4 and 6 of commonly assigned 10/600,007. The issue of priority under 35 U.S.C. 102(g) and possibly 35 U.S.C. 102(f) of this single invention must be resolved.

Since the U.S. Patent and Trademark Office normally will not institute an interference between applications or a patent and an application of common ownership (see MPEP Chapter 2300), the assignee is required to state which entity is the prior inventor of the conflicting subject matter. A terminal disclaimer has no effect in this situation since the basis for refusing more than one patent is priority of invention under 35 U.S.C. 102(f) or (g) and not an extension of monopoly.

Failure to comply with this requirement will result in a holding of abandonment of this application.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 10 is directed to conjugates comprising one or more aptamers linked to a drug and having the formula shown in the claim. This claim is indefinite because it requires a drug to be present but in the formula the drug component can be zero. Claims 11-18 are indefinite due to their dependence from claim 10.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4, 6 and 10-18 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The claims are directed to aptamer-drug conjugates, including conjugates that comprise multiple aptamers joined through a linker to multiple drugs. In specific embodiments the aptamers target PSMA, the drug is a vinca alkaloid that is desacetylvinblastine-3-carboxhydrazide and the linker comprises amines, dendrimers or comb polymers. The claims encompass a broad genus of conjugates comprising multimeric aptamers conjugated to multimeric drug components, including those wherein the aptamers are targeted to tumor cells.

The specification provides the structures of cytotoxins, the structures of linkers usable for the production of conjugates and provides prophetic teachings of the isolation of aptamers and synthesis of conjugates. However, the specification does not disclose the structure of any aptamers nor any aptamer- or multimeric aptamer-drug conjugates. Neither the prior art nor the

specification provides representative samples of the genus of compounds encompassed by the claims.

Specific embodiments of the claims encompass aptamers or aptamer multimers that are targeted to PSMA; no structures of such aptamers are disclosed in the specification. Because aptamers are discovered empirically, the structures of aptamers known from the prior art to target a particular protein would not lead the skilled artisan to the structures of aptamers having the function of binding PSMA.

In order for the written description provision of 35 USC 112, first paragraph to be satisfied, applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed. For example, MPEP 2163 states in part,

> "An adequate written description of a chemical invention also requires a precise definition, such as by structure, formula, chemical name, or physical properties, and not merely a wish or plan for obtaining the chemical invention claimed. See, e.g., *Univ. of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 927, 69 USPQ2d 1886, 1894-95 (Fed. Cir. 2004) (The patent at issue claimed a method of selectively inhibiting PGHS-2 activity by administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product, however the patent did not disclose any compounds that can be used in the claimed methods. While there was a description of assays for screening compounds to identify those that inhibit the expression or activity of the PGHS-2 gene product, there was no disclosure of which peptides, polynucleotides, and small organic molecules selectively inhibit PGHS-2. The court held that "[w]ithout such disclosure, the claimed methods cannot be said to have been described.")."

The skilled artisan cannot envision the detailed structure of the encompassed aptamer or multimeric aptamer conjugates, including those that bind to PSMA, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Therefore, the full breadth of the genus of aptamer- and multimeric aptamer-drug conjugates encompassed by the claims do not meet the written description provision of 35 USC 112, first paragraph.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 2, 4, 6, 10, 11, 13 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Hicke et al. (US 6,232,071, cited on IDS of 12/04).

The claimed invention is directed to aptamer-toxin conjugates comprising aptamers conjugated to cytotoxic moieties that can be small molecule chemotherapeutic agent and can be covalently conjugated. In some embodiments the aptamers target tumor cells and the linker comprises nucleophilic or electrophilic moieties.

Hicke et al. disclose nucleic acid ligands (aptamers) to tenascin-C, including conjugates with therapeutic agents including cytotoxic agents. At column 11 Hicke et al. disclose that the therapeutic agent can be covalently attached to the nucleic acid ligand

with or without a linker and are useful in targeting diseases, such as cancer, that are associated with expression of tenascin-C. At column 7, Hicke et al. disclose that a preferred linker is hexylamine.

Therefore, Hicke et al. disclose all limitations of and anticipate claims 1, 2, 4, 6, 10, 11, 13 and 16.

Claims 1, 2, 4, 6, 10, 11, 13, 14 and 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Warren (WO 99/30561, cited on IDS of 12/04).

Warren discloses at pages 17-18 prodrugs comprising an aptamer and a drug joined by a linker. Warren discloses at pages 26-27 that the drugs include vinca alkaloids. Example 5 describes use of the disclosed prodrugs to target cancerous cells.

Thus, Warren discloses all limitations of and anticipates claims 1, 2, 4, 6, 10, 11, 13, 14 and 16.

Claim 1 is rejected under 35 U.S.C. 102(e) as being anticipated by Elmaleh et al. (US 2003/0049203).

Claim 1 is directed to an aptamer-toxin conjugate therapeutic agent that comprises a targeting moiety conjugated to a cytotoxic moiety. The term "targeting moiety" is not explicitly defined by the specification and thus is interpreted to include any molecule capable of directing the cytotoxic moiety to a cell.

Elmaleh et al. disclose constructs comprising a targeting moiety, a nucleic acid and a payload, illustrated in figure 2. The term payload is disclosed at paragraphs 42 and 104 as including drugs such as chemotherapeutic agents.

Thus, Elmaleh et al. disclose all limitations of and anticipate claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 2, 4, 6 and 10-18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Warren as applied to claims 1, 2, 4, 6, 10, 11, 13, 14 and 16 above, and further in view of Holmes (Expert Opinion on Investigational Drugs, 2001), Apelgren et al. (Cancer research 1990) and Virtanen et al. (US 5,997,861).

Claims 1, 2, 4, 6, 10, 11, 13, 14 and 16 are described in the 102 rejection over Warren. Claim 12 recites that the aptamer targets PSMA, claim 15 recites a particular structure of the alkaloid vinblastine and claims 17 and 18 recite particular linkers, including dendrimers.

The teachings of Warren are described in the 102 rejection over this reference, including aptamer-drug conjugates wherein the drug can be a vinca alkaloid. In table 4 Warren specifically teaches that the drug can be the vinca alkaloid vinblastine. At page 7 Warren teaches that aptamers have been used as an alternative to antibodies for the purpose of targeting therapeutic agents to cells. Warren does not explicitly teach aptamers targeted to PSMA, the use of the vinblastine analog desacetylvinblastine-3-carboxhydrazide or the use of linkers that comprise dendrimers.

Holmes teaches that PSMA is a transmembrane protein specific to prostate epithelial cells that is expressed at increased levels in cancerous cells. Holmes further teaches that this protein is an ideal sentinel molecule for targeting prostate cancer cells.

Apelgren et al. teach that antibodies conjugated to 4-desacetylvinblastine-3-carboxhydrazide were known in the art to regress adenocarcinoma and squamous carcinoma xenografts in athymic nude mice. Apelgren et al. extend the use of such conjugates to the treatment of ovarian cancer. Apelgren et al. teach that the use of the conjugated drug increased the survival of tumor bearing mice over treatment of the drug alone or a non-antigen binding immunoconjugate.

Virtanen et al. teach complexes containing a binding molecule such as an antibody, a joining component and a therapeutic molecule such as a drug. At column

10 Virtanen et al. teach that the joining component may be a bifunctional linker and may be a dendrimer type polymer.

It would have been obvious to one of ordinary skill in the art at the time of invention to make aptamer-drug conjugates as taught by Warren using an aptamer that targets PSMA. It would have been further obvious to use desacetyl-3-carboxhydrazide as the drug component of the conjugate and to use a dendrimer as the linker component. Holmes provides a motivation to target PSMA with therapeutic agents, teaching that this protein is preferentially expressed in prostate tissue and expressed at increased levels in cancerous cells. Warren explicitly teaches vinblastine as the drug component of an aptamer-drug conjugate and Apelgren et al. provide a motivation to use desacetylvinblastine-3-carboxhydrazide by teaching that immunoconjugates comprising this drug increase survival time of tumor bearing mice over those receiving the drug alone. Based the teachings of Virtanen et al. one of ordinary skill in the art would recognize that the use of a dendrimer linker is mere design choice made by the person of ordinary skill in order to produce a conjugate with the optimum properties for the desired application. One of ordinary skill in the art would have had a reasonable expectation of success in targeting PSMA with the conjugates taught by Warren because Warren teaches aptamer-drug conjugates, their general applicability and methods of synthesis. One of ordinary skill in the art would have had a reasonable expectation of success in making aptamer-drug conjugates comprising desacetylvinblastine-3-carboxhydrazide or dendrimers because Warren teaches the production of aptamer-drug conjugates, Apelgren et al. teach the synthesis of

conjugates comprising desacetylvinblastine-3-carboxhydrazide and Virtanen et al. teach that dendrimers are a known linking moiety that can be incorporated into a conjugate using known synthetic methods.

Thus, the invention of claims 1, 2, 4, 6 and 10-18 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The central FAX Number is 571-273-8300.

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Tracy Vivlemore
Examiner
Art Unit 1635

TV
June 29, 2006

JAMES SCHULTZ, PH.D.
PRIMARY EXAMINER